CHAPTER 226

# SEX HORMONES AND HUMAN CARCINOGENESIS: EPIDEMIOLOGY

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Because of the central role that the hormonal milieu plays in various carcinogenic processes, it is essential that clinical endocrinologists be aware of malignancies to which their patients may be predisposed, either because of the nature of their illness or because of the nature of the hormonal therapy being instituted.

## CARCINOGENESIS AND ENDOGENOUS SEX HORMONE STATUS

Endogenous hormone status has long been thought to be an important factor in the etiology of a number of human malignancies, and this belief has been based on animal carcinogenesis studies, (see chap 225), the responsiveness of a number of tumors to hormonal manipulation (see chaps 227 and 228), the relationship of risk of certain tumors to a variety of reproductive and other factors thought to influence hormonal status, and the simple fact that some organs depend on hormonal status for their normal function.[1] Speculation about a hormonal cause has

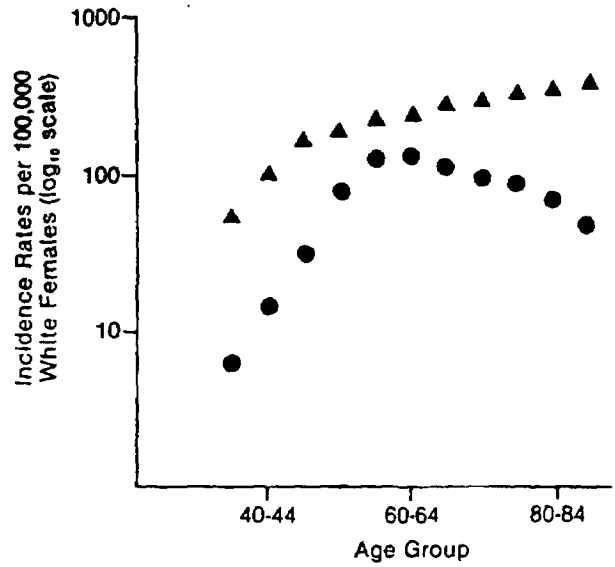


**FIGURE 226-1.** Average annual breast cancer (▲) and endometrial cancer (●) incidence rates for white females. (SEER data, 1973–1977). (*From Hoover RN. In Harris CE, ed. Biochemical and molecular epidemiology of cancer. NY: Alan R Liss Inc., 1986:313.*)

focused on malignancies of the female breast and the reproductive tract. However, some evidence for hormonal carcinogenesis has been noted for a variety of other tumors, including prostate, testis, thyroid, and gallbladder cancers, and malignant melanoma. Despite these long-standing suspicions, with the possible exception of endometrial cancer, there has been little success in identifying the specific hormonal factors that might be responsible for these tumors.

## CARCINOGENESIS AND EXOGENOUS SEX HORMONE THERAPY

Within the last 40 years, a new element in the area of hormonal influences on cancer risks has been added, that of exogenous sex hormone exposure. Pharmacologic levels of estrogens, progestins, androgens, and pituitary trophic hormones, alone or in combination, have been administered to large segments of the population for various reasons. These large-scale "natural experiments" have provided more specific insights into the relationship between hormonal factors and several different malignancies.[2] Moreover, enthusiasm has grown for the widespread treatment of relatively healthy segments of the population (e.g., oral contraception, menopausal replacement therapy). There is considerable interest in the use of estrogens for post-menopausal prevention of osteoporosis and osteoporotic fractures (see chaps 65 and 102).[3] Some evidence supports the long-suspected potential of menopausal estrogens to prevent clinical coronary heart disease.[4] Because of this enthusiasm, appropriate evaluations of the carcinogenic consequences of these exposures has become important to public health, as well as to understanding the biology of the tumors involved.

**TABLE 226-1**
**Relative Risks (RR)* of Endometrial Cancer Associated With Menopausal Estrogen Use From Selected Case-Control Studies**

| Reference | Source of Controls | Overall RR | RR Among Long-term Users† |
|---|---|---|---|
| Ziel[9] | Health plan | 7.6 | 13.9 |
| Mack[9] | Retirement community | 5.6 | 8.8 |
| Gray[10] | Private practice | 3.1 | 11.6 |
| Antunes[11] | Hospital patients | 4.3 | 15.0 |
| Weiss‡[12] | Community | 7.9 | 14.3 |
| Hulka[13] | Gynecology patients | 1.8 | 4.1 |
| Shapiro[14] | Hospital patients | 3.9 | 6.0 |
| Kelsey[15] | Hospital patients | 1.6 | 8.2 |

* Risk of cancer relative to a risk of 1.0 for women who never used menopausal estrogens.
† Definition of *long-term* varied from ≥5 to ≥10 years
‡ Refers to continuous users.

## ENDOMETRIAL CANCER

### ENDOGENOUS FACTORS IN ENDOMETRIAL CANCER

The cancer for which the evidence for both an endogenous and an exogenous hormonal cause is best established is endometrial cancer.

Various factors related to endogenous hormone production have been associated with endometrial cancer.[5] Medical conditions related to increased risk include functional (estrogen-secreting) ovarian tumors, the polycystic ovary syndrome, diabetes mellitus, and hypertension. Reproductive factors also have consistently been found to be related to increased risk, including nulliparity and a late natural menopause. Some dietary factors also seem to influence risk, including obesity as a risk factor and vegetarian diet as a possible protective factor.[6] Age, a determinant of levels of most endogenous hormones, also influences endometrial cancer risk in a unique manner. Endometrial cancer rates are extremely low under the age of 45, rise precipitously among women in their late 40s and throughout their 50s (much more dramatically than for other tumors) and then decline from about age 60 onward (Fig 226-1).

### EXOGENOUS SEX HORMONES AND ENDOMETRIAL CANCER

Exogenous hormones also have been linked to endometrial cancer.[7]

#### ESTROGENS AND ENDOMETRIAL CANCER

Estrogen replacement therapy of the menopause for two years or longer is associated with an excess *relative risk* (RR) of endometrial cancer. Table 226-1 shows estimated RRs (i.e., the risk of the disease among those exposed to estrogen therapy compared with the risk among those not exposed).[8–15] The relative risk among users compared with nonusers ranges from two- to eightfold. It increases even further with long duration of use and with high average daily doses. Thus far, every type of estrogen that has been investigated has shown this relationship, including conjugated equine estrogens, ethinyl estradiol, and diethylstilbestrol (DES). The highest risk occurs among current users. The risk declines with each year after cessation of use, although apparently there still is some residual excess risk even ten years after cessation. The risk is highest for early-stage malignancies, but there is a two- to threefold excess risk for the advanced stages of disease as well. (After early positive studies, some investigators questioned whether or not the association might be spurious because of the opportunities for enhanced detection of latent endometrial cancer among estrogen users. Various approaches yielded evidence consistent with a causal relationship between menopausal estrogen treatment and an increased risk of endometrial cancer.)

#### EFFECT OF ESTROGEN–PROGESTERONE IN SEQUENCE

There has been a profound trend away from unopposed estrogen treatment of menopausal symptoms and toward treat-

ment with a sequence of an estrogen which is then combined with a progestin. There is substantial evidence that such cyclic treatment reduces the frequency of hyperplasias and atypical hyperplasias associated with unopposed estrogen treatment.[16] The first epidemiologic data on risk of endometrial cancer itself has appeared. While as yet based on small numbers of observations, use of the combined regimen exclusively does not appear to be related to excess endometrial cancer risk. However, such use also does not appear to prevent the background or "expected" numbers of cancers, nor does it remove the excess risk induced by any prior use of the estrogen-only regimen.[16a]

### ORAL CONTRACEPTIVES AND ENDOMETRIAL CANCER

Oral contraceptives also have been studied extensively in relation to endometrial cancer, following the observations in the early 1970s that young women receiving sequential oral contraceptives (particularly dimethisterone and ethinyl estradiol [Oracon]) were developing endometrial cancer.[17] Subsequent investigations estimated that such women were at a two- to eightfold excess risk of this tumor. On the other hand, nonsequential, combination oral contraceptives clearly are related to decreased risks of endometrial cancer (Table 226-2). Relative risks of 0.4 to 0.5 have been observed, indicating a 50% to 60% protection associated with such use.[18–22] There is also some evidence of increased levels of protection with increased years of use. The effects of stopping use are unclear. Two studies have noted that the protection was substantial among current users and subsided after cessation.[20,22] These studies, however, disagreed on the duration of protection after stopping. In addition, most studies have observed profound interaction between other endometrial cancer risk factors and the associations with combination oral contraceptive use. Specifically, the protective effect is absent among the obese,[23] among long-term estrogen users, and among the multiparous. Although the same interactions have not been found in all studies, these observations would be consistent with a number of these risk factors operating through common or highly correlated hormonal mechanisms.

**TABLE 226-2**
**Relative Risks (RR)* of Endometrial Cancer Associated With Combination Oral Contraceptive Use From Five Case-Control Studies**

| Reference | Source of Controls | Overall RR | RR Among Long-term Users† |
|---|---|---|---|
| Weiss[18] | Community | 0.5 | |
| Kaufman[19] | Hospital patients | 0.5 | 0.3 |
| Hulka[20] | Community | 0.4 | 0.3 |
| Henderson[21] | Neighborhood | 0.5 | 0.2 |
| CDC‡[22] | Community | 0.5 | 0.6 |

* Risk of cancer relative to a risk of 1.0 for women who never used oral contraceptives.
† Definition of *long-term* varied from ≥4 to ≥5 years.
‡ Centers for Disease Control.

## MECHANISMS OF ACTION

A unified theory of how these risk factors operate has been proposed (Fig 226-2).[24] Most known risk factors are associated with increased levels of circulating estrogens, particularly estrogens not bound to protein. Clearly, also related are the age effects, and the use of combination oral contraceptives, which probably modify the increased risk associated with estrogen level through the modulating effects of progestogens. Furthermore, although nulliparity, diabetes, hypertension, and race have not yet been included in this scheme, they possibly will be as our knowledge of basic endocrinology expands.

The model suggests several promising lines of future clinical, epidemiologic, and laboratory research. The way that obesity affects the peripheral conversion of estrogen precursors deserves more attention. When in a woman's life does obesity matter most? Some data suggest that weight loss decreases circulating estrogens; other data do not. Does the number of adipocytes or their content determine peripheral conversion? What accounts for the reduced risk among vegetarians? The effects of progesterone also deserve further study, including resolving whether the protection given by combination oral contraceptives is transient, and measuring the effects of the new combination-type menopausal estrogen regimen.

Perhaps most important to our understanding of carcinogenesis will be the clarification of the precise mechanism by which circulating estrogens produce endometrial cancer. Several possibilities have been proposed: that estrogens are complete carcinogens themselves; that they promote initiated cells; or that they simply stimulate growth and, thereby, offer a greater opportunity for abnormal cells to arise or for carcinogens to act on vulnerable genetic material. The epidemiologic evidence strongly favors the argument that estrogens act at a relatively late stage in the process of carcinogenesis. If estrogens are promoters, however, no initiators of the process are readily apparent.

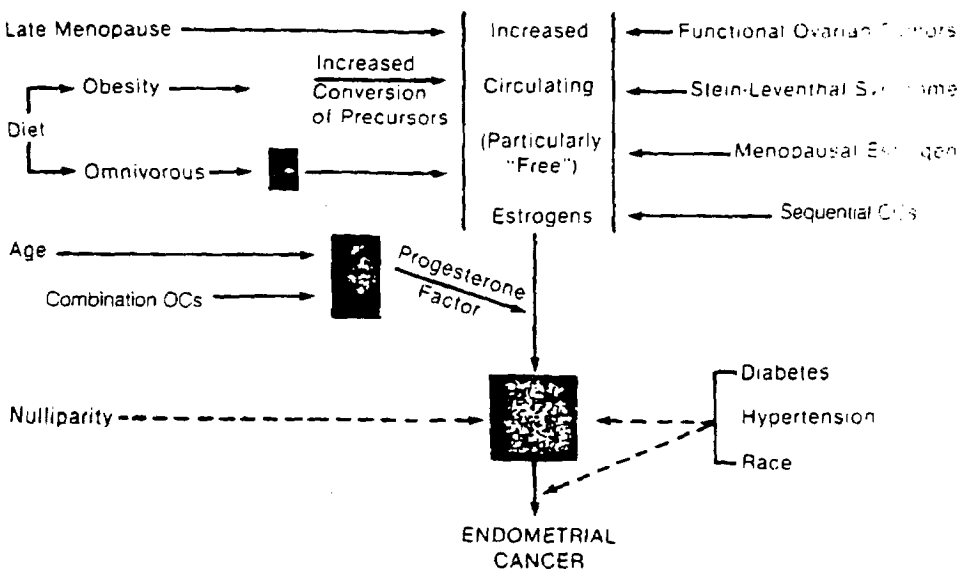


**FIGURE 226-2.** Risk factors for endometrial cancer and their possible modes of action. (*From Hoover RN. In Harris CE, ed. Biochemical and molecular epidemiology of cancer. NY: Alan R Liss Inc., 1986:313.*)

## BREAST CANCER

The hormonal etiology of breast cancer is well accepted, but no unified model for the mechanism exists. Several hormonal hypotheses have been suggested, but supporting data are lacking.

### ENDOGENOUS FACTORS IN BREAST CANCER

The importance of the ovary in breast cancer etiology is demonstrated by its relationship to a number of breast cancer risk factors.[25] Earlier ages at menarche are associated with high risks of breast cancer. Similarly, later ages at natural menopause also are associated with elevated risks. Surgical removal of the ovaries before natural menopause reduces risk of breast cancer, and the earlier the operation, the lower the risk. The shape of the age–incidence curve for this disease (see Fig 226-1) has been interpreted as showing that the onset of ovarian activity early in life determines the slope of the curve, and that a reduction in this ovarian factor around the time of the menopause is responsible for the change in slope of the curve at about age 50.

Other risk factors for breast cancer also have been well established.[26] A history of breast cancer in a first-degree relative elevates a woman's risk of contracting breast cancer two- to fivefold. Historical observations of a protection against breast cancer associated with an increase in parity were found to reflect the influence of the age at first birth. A woman who has her first child after the age of 30 has approximately two- to threefold the risk of breast cancer of a woman who had her first child under the age of 18. Nulliparous women have approximately the same risk as those women who had their first child at age 30, whereas women having a first birth after this age actually experience a greater risk than do nulliparous women. Investigations have implied that increased parity may indeed diminish the risk of breast cancer, even when controlled for age at first birth.[27] Benign breast disease, particularly that containing hyperplastic or dysplastic elements, places a woman at two- to fivefold excess risk of subsequent breast cancer.[28] Obesity also appears to be a risk factor for breast cancer, although both the consistency with which this is found and the magnitude of the elevation in risk are considerably less than those observed for endometrial cancer.

### INFLUENCE OF DIET

Diet is strongly suspected of playing a role, because of worldwide differences in breast cancer rates. Oriental populations have rates five- to sixfold lower than those seen in the United States and Western Europe. Migrants from Japan and China to the United States experience risks that rise toward the Caucasian levels over the course of three generations of residence within the United States. While some direct support for these dietary hypotheses has been proposed,[28a] a number of studies have found no relationship, and the entire area remains controversial.[29,30,30a,30b]

**TABLE 226-3**
**Relative Risk (RR)* of Breast Cancer Associated With Menopausal Estrogen Use From Seven Recent Case-Control Studies**

| Reference | Source of Controls | Overall RR | RR Among Long-term Users† |
|---|---|---|---|
| Ross[38] | Community | 1.1 | 1.9 |
| Hoover[39] | Health plan | 1.4 | 1.7 |
| Brinton[40] | Mammography screening program | 1.0 | 1.5 |
| Hulka[41] | Hospital patients | 1.5 | 0.7 |
| | Community | 1.6 | 1.7 |
| Hiatt‡[42] | Health plan | 0.7 | 2.8 |
| Kelsey[43] | Hospital patients | 1.0 | 0.7 |
| Kaufman[43] | Hospital patients | 0.9 | 0.7 |

* Same as Table 226-1.
† Various definitions of *long-term*.
‡ Study limited to women having undergone bilateral oophorectomy.

### HYPOTHESES FOR THE CAUSATION OF BREAST CANCER

It frequently is speculated that a unifying hormonal hypothesis for breast cancer is possible, because even the nonovarian risk factors actually may operate through a hormonal mechanism. Perhaps the simplest of these models is that breast cancer risk reflects total lifetime, or perhaps early life, dose of estrogens.[31,32] Related to this is the unopposed-estrogen hypothesis, which also assumes that estrogens are the important risk factor, but emphasizes the relative protective role of progesterone.[33] The estrogen-fraction hypothesis also assumes estrogens to be hazardous, but adds that a woman's risk reflects the proportions of different estrogens, because they have different carcinogenic potentials.[34] The estrogen-window hypothesis suggests that in a relatively short period after menarche, and then again in another short period before menopause, estrogen exposure, unopposed by progesterone, might cause an enhanced susceptibility to other carcinogenic influences on breast tissue.[35] A recent hypothesis holds that the proportion of free versus protein-bound estrogen determines a woman's breast cancer and endometrial cancer risk.[36] Finally, pituitary hormones and prolactin in particular have been suggested as being primarily involved in breast carcinogenesis.[36a]

Confirmation for these hypotheses has been sought by measuring levels of various hormones—first, in breast cancer patients and controls either at the time of diagnosis or at some time before and, second, in women with different levels of known risk factors, to determine whether the risk factors operate through specific hormones. These laboratory–epidemiologic studies do not rule out any of the proposed models of endogenous hormone effects as a partial explanation, nor do they support any one model as the unified explanation, perhaps because the women are being tested at ages other than those critical for breast cancer risk modification. Or, perhaps, the premise of a unifying hypothesis is incorrect.

Thus, although the evidence that breast cancer is a tumor of hormonal etiology is overwhelming, the specific endogenous hormones involved and their relative roles remain elusive.

### EXOGENOUS SEX HORMONES AND BREAST CANCER

The role of exogenous hormones is even less defined. In particular, it is still not clear whether the use of estrogens postmenopausally or of oral contraceptives affects breast cancer risk

#### ESTROGENS AND BREAST CANCER

The widespread use of noncontraceptive estrogens seems to be an ideal natural experiment through which to evaluate some of the more prominent hormonal hypotheses about breast cancer etiology. Unfortunately, the relationship remains controversial because of conflicting evidence. A retrospective cohort study reported in 1976 suggested a relatively small overall excess risk (30%) among conjugated estrogen users, which reflected a twofold excess risk among long-term users.[37] Over the ensuing decade, seven case-control studies and one follow-up investigation without significant methodologic flaws addressed this observation (Table 226-3).[38–45] Three of the case-control studies are positive, with evidence of dose–response and an excess risk of up to twofold among long-term users.[38–40] Two studies show some evidence of an association, but also contain some incon-

sistencies in dose-response relationships or subgroup analyses.[41,42] Two studies clearly are negative, with no evidence of association with long-term use.[43,44] The two negative studies are the only two that utilized a hospital comparison group, rather than the general population. If hospitalized women more commonly used replacement estrogens than women in the general community, these studies would underestimate any increase in risk. Some studies have suggested that the association may be stronger among older women, those having undergone an oophorectomy, or those with a family history of breast cancer. However, these subgroup findings have not been consistent. Perhaps the most consistent finding is an enhanced excess risk associated with estrogen use among women with surgically confirmed benign breast disease. These findings have emerged from several of the case-control studies and refer to the entire population in the foregoing follow-up study.[45] More recent studies have continued to produce conflicting evidence.[45a-c] The latter study may be of particular note, since it is the first to address the issue of breast cancer risk associated with the use of the combined estrogen-cyclic progestin regimen.[45c] In this study, there was an overall increase of 70% in breast cancer risk among those using replacement estrogens for more than nine years. In contrast to the pattern for endometrial cancer, this excess was not reduced in those also receiving cyclic progestins. In fact, the risk was higher and appeared earlier in these women than in those receiving the estrogen-only regimen.

Noncontraceptive hormonal exposures, other than the use of menopausal estrogen, are relatively rare and generally have not been investigated. A notable exception is the risk of breast cancer among women who took diethylstilbestrol during a pregnancy to prevent a spontaneous abortion. Three clinical trials of diethylstilbestrol use have been evaluated for long-term sequelae, and three follow-up studies of exposed women have also been reported.[46] Two of the three clinical trials showed evidence of excess breast cancer risk. Two of the cohort studies revealed overall excesses of 50%, with evidence of increasing risk with increasing interval from exposure, rising to 70% after 15 years of follow-up and 2.5-fold after 30 years.

While considerable controversy remains concerning causality, practically, it would seem prudent to assume that high cumulative doses of noncontraceptive estrogens are related to a 50% to twofold excess breast cancer risk after an interval of about 15 years since first exposure, and one should make risk-benefit decisions about drug use based on this assumption.

### ORAL CONTRACEPTIVES AND BREAST CANCER

The extensive use of oral contraceptives (see chaps 106 and 107) since they were licensed for use in the United States also seems to be a promising natural experiment, as well as an important public health issue. Overall, the results of such studies have been much more consistent than those for menopausal estrogen use, although these results are somewhat surprising. Because oral contraceptives so clearly alter the hormonal milieu, most investigators had predicted that oral contraception, particularly of long duration, would have a substantial impact on subsequent breast cancer risk. Whether this effect would be hazardous or beneficial was hotly debated. However, most studies have found essentially no relationship between the use of oral contraceptives and the risk of breast cancer either overall or among long-term users.

**Oral Contraceptives in the Older Woman.** There are two notable exceptions to the overall absence of effect. First, women who use oral contraceptives at older ages (40s and early 50s) appear to have an excess risk. Contraceptives used at these ages counter the natural decline in endogenous hormones and often cause an extension of menstrual activity, so the excess risks are like those seen with a later natural menopause. Because of the cardiovascular complications of oral contraceptive use, prominent among users over age 40, these medications now are seldom used in this manner; thus, the effect may only be of historical interest.

**Oral Contraceptives Used Extensively at an Early Age.** The second exception to the overall absence of effect is among women who use oral contraceptives extensively either at a young age or before having their first child. In the early 1980s, three studies suggested an excess risk associated with such a pattern of use.[47,48,48a] At the time, two large case-control studies had contrasting evidence. In particular, a large study of young women with breast cancer, focusing primarily on oral contraceptive use, produced no evidence of a hazardous effect of long-term use either among those using oral contraceptives before the age of 25 or before having a first child.[48] A series of studies prompted by these concerns have been completed. The first two to be published have added to the concern over increased risk of breast cancer among women who used oral contraceptives extensively at a young age.[49a,49b] In the British study, the relative risk rose to 1.74 for breast cancer among women under age 36 who had used oral contraceptives for more than eight years.[49b]

**Oral Contraceptives and Benign Breast Disease.** A number of studies have noted significant protection against benign breast disease with oral contraceptive use. The protection is limited to current or recent use, with the effect disappearing one to two years after cessation. The magnitude of the protective effect also seems directly related to the dose of the progestin in the medication. Conflicting evidence exists on whether or not the effect applies to the pathologic subtypes of benign breast disease that are risk factors for the subsequent development of breast cancer. Because of the transitory nature of the protective effect and questions about the pathology involved, the biologic relevance of this association to breast cancer risk remains unclear.

### FUTURE IMPERATIVES

Clearly the long-term consequences of oral contraceptive use on breast cancer risk will remain a research subject for many years. Only now are substantial numbers of women who used oral contraceptives for five or more years early in their reproductive lives entering the ages of high breast cancer risk. If the timing of the mammary effects of oral contraceptives resembles that of the endogenous hormonal risk factors and of exogenous estrogens, effects not detected before may yet become apparent. Moreover, if the age at exposure or the presence of other breast cancer risk factors (e.g., family history) modify the effect of contraceptive use, only large-scale and long-term efforts will yield precise estimates of these interactive effects. There is little question that such effects are of major public health importance because of widespread exposure to these compounds. Thus, although the data from a variety of studies are encouraging, the final conclusion on long-term sequelae of oral contraceptive use must be postponed.

The advent of enthusiasm for cyclic estrogen-progestogen treatment of the menopause offers the opportunity to investigate an exposure of particular relevance to a number of the etiologic theories concerning the hormonal basis of breast cancer. Such studies also would seem to warrant a high priority, both on this basis and by virtue of the sudden onset of treatment of a large population of healthy women with this essentially unstudied drug combination therapy.

## OVARIAN CANCER

Compared with cancers of the endometrium and breast, much less is known about risk factors for ovarian cancer. Until the late 1970s, it was little studied, but several extensive epidemiologic investigations have been undertaken recently.

### INFLUENCING FACTORS IN OVARIAN CANCER

Only a few risk factors for ovarian cancer have been identified from these investigations, and they account for only a small proportion of the disease, but the few factors consistently identified clearly imply a hormonal etiology for this malignancy.[50] First of all, parity is protective, with the risk of the disease being highest among nulliparous and declining by 70% among those with three or more live births. Independent of nulliparity, there is a consistent finding of a three- to fivefold excess risk among women who have had medical consultation for infertility. Few other risk factors reflecting endogenous hormonal status have been identified for ovarian cancer, and none with any consistency among studies.

### EXOGENOUS ESTROGENS AND OVARIAN CANCER

Exogenous estrogens have been studied in various case-control and follow-up studies over the past seven years. Most studies have found no consistent association between menopausal estrogen use and the risk of ovarian cancer. The overall relative risks in these studies have been close to 1.0 and yielded no evidence of higher risks for longer durations or higher doses of estrogen. One investigation found an increased risk of ovarian cancer among women who received both conjugated estrogens and diethylstilbestrol for the treatment of menopausal symptoms.[51] However, the numbers of cases in this study were limited and the finding has not been confirmed.

#### ORAL CONTRACEPTIVES AND OVARIAN CANCER

Oral contraceptives, by contrast, appear to exert a marked protective effect. The effect seems to be related to duration, with those using oral contraceptives for more than five years having an approximately 50% to 70% reduced risk of the disease.[52]

The encouraging nature of this result has overshadowed some inconsistencies among individual studies. Whether these differences reflect chance biases in some studies, the influences of varying patterns of use between studies, or meaningful biologic interactions remains unclear. Critical comparisons of the existing studies and new data may enhance our understanding of ovarian carcinogenesis and clarify risk–benefit issues, particularly as demographic patterns of oral contraceptive use continue to change. In particular, the influence of cessation of use on risk for ovarian cancer could use more study.

**Possible Mechanism of Protection.** The increased risk associated with infertility coupled with the decreased risk associated with increased parity and the extended use of the oral contraceptives implicates gonadotropin stimulation of the ovary in its carcinogenesis. Decreased stimulation should reduce the risk, and those conditions associated with enhanced stimulation should elevate the risk. If this unifying hypothesis is supported by further evidence, it would have direct implications on the consequences of several current trends in endocrine therapy.

**TABLE 226-4**
**Relative Risk (RR)* of Cervical Neoplasia Among Long-Term Oral Contraceptive Users From Five Recent Investigations**

| Reference | Disease Type† | Source of Comparison Group | Relative Risk (Years of Use) |
|---|---|---|---|
| Harris[56] | D + C | Hospital patients | 2.1 (≥10) |
| Swan[57] | D + C | Health plan members | 1.5 (≥7) |
| Vessey[58] | D + C + I | IUD users | 2.3 (≥8) |
| WHO[59] | I | Hospital patients | 1.5 (≥5) |
| Brinton[60] | I | Neighborhood | 1.8 (≥10) |

* Same as Table 226-2.
† D, dysplasia; C, carcinoma in situ; I, invasive.

## CANCER OF THE UTERINE CERVIX

### RISK FACTORS AND CERVICAL CANCER

Most findings from studies of cervical cancer are consistent with a venereally transmitted agent being primarily involved.[53] The two major risk factors that elevate a woman's risk of this malignancy are a large number of different sexual partners and an early age at first intercourse. In addition, among women with only one sexual partner, the more sexual partners her mate has had, the higher her risk of cervical cancer. Clinical, laboratory, and epidemiologic work on papilloma viruses suggests that these agents may be the key infectious factor in the etiology of this disease.[54]

The strength of sexual, social, and specific infectious risk factors have tended to obscure other factors that might contribute to this disease. For example, it has been observed that cigarette smoking is a risk factor, even after control for sexual variables.[55] The presence of tobacco metabolites in cervical mucus provides a plausible biologic rationale for the role of tobacco.

### ORAL CONTRACEPTIVES AND CERVICAL CANCER

Potential hormonal risk factors for cervical cancer have not been systematically sought, but the cervix is a target organ for several of the sex hormones and, therefore, a likely candidate for the modification of tumor incidence by hormonal factors. Recent studies linking the risk of cervical disease to exogenous hormonal exposures are particularly provocative. A series of case-control and follow-up studies have linked oral contraceptive use to cervical intraepithelial neoplasia and frankly invasive cervical carcinoma.[56–60] These studies have found a risk that rises with the duration of use to approximately twofold among long-term users of oral contraceptives (Table 226-4). At first, these associations were suspected to be spurious, simply reflecting the correlated effects of the sexual and social-class risk factors for this disease, but increasingly sophisticated studies have supported the likelihood of an association. Indeed, of all the cancer sites for which oral contraception might increase risk, the current data point to the uterine cervix as the site of greatest concern.

### IN UTERO DIETHYLSTILBESTROL EXPOSURE AND CERVICAL CANCER

Most recently, a systematic follow-up of women who were exposed in utero to diethylstilbestrol has revealed an increased incidence of cervical intraepithelial neoplasia among these women compared with women unexposed to the drug.[61] The data are preliminary and need confirmation, but further support the belief that the uterine cervix is an endocrine target organ whose neoplastic potential may depend upon hormonal influences.

## OTHER GYNECOLOGIC CANCERS AND EXOGENOUS SEX STEROIDS

The causal relationship between diethylstilbestrol exposure in utero and the subsequent occurrence of *clear cell carcinomas of the vagina and cervix* is well established. This relationship was first noted in the early 1970s and, subsequently, a registry was established that, thus far, has accumulated over 400 cases of this malignancy in women born after 1940.[62] Current estimates of the risk of this malignancy among those exposed to the drug are about 1:10,000. In almost all documented cases, the treatment with diethylstilbestrol had started before the 18th week of pregnancy, and there is evidence that the earlier in pregnancy the treatment was initiated, the greater the risk. Dose and duration-response relationships remain somewhat less clear. An interest-

ing feature of this malignancy is the attack rate by age. The cases seem to be diagnosed primarily from preadolescence through age 30. The slope of the attack rate curve is particularly steep from age 11 through age 20. This would seem to imply that the onset of puberty is required for expression of the carcinogenic effect and may indicate a promotional role for endogenous hormones in completing the carcinogenic effect of diethylstilbestrol.

*Trophoblastic disease* (see chaps 113 and 114) has been related to oral contraceptive use in one investigation.[63] Women with benign hydatidiform mole were twice as likely to develop invasive mole if they had used oral contraceptives before their human chorionic gonadotropin levels returned to normal following the benign mole. This finding remains unconfirmed, but suggests that the increased risk of invasive trophoblastic disease may be linked to the use of oral contraceptives.

## MALE GENITAL CANCERS AND SEX STEROIDS

The roles of sex hormones in male genital cancers have not been well studied, but there is substantial reason to believe that hormonal factors do operate.

Because of its relative rarity, *testicular cancer* has not often been the subject of major analytic epidemiologic investigations (see chap 126). Recently, studies of testicular cancer in relatively young men, and other studies of cryptorchidism (a major risk factor for this tumor), have implied that high levels of circulating estrogens (from either an endogenous or exogenous source) in a pregnant woman could place a male offspring exposed in utero at a high subsequent risk of these conditions.[64] These preliminary findings indicate the need for attention to hormonal risk factors for testicular cancer.

Although *prostate cancer* is a common malignancy among men in the United States, little is known with certainty about its etiology in humans. Many investigators hypothesize a hormonal influence based on the roles of sex hormones in the development and maintenance of normal prostatic function, experimental evidence, the responsiveness of prostatic cancer to therapeutic hormonal manipulation, and limited clinical data. It also has been speculated that some of the descriptive risk factors for this disease, including racial and ethnic variation, may operate through a hormonal mechanism. Prominent hormonal hypotheses suggest an increased risk of prostatic cancer caused by increased levels of testosterone, decreased levels of estrogen, increased levels of prolactin, or some combination of these.[65,66] Despite the frequency of the malignancy and the concerns over a hormonal etiology, few epidemiologic data exist to address these hypotheses. This lack of analytic studies stems partly from doubts that hormonal patterns in patients with prostatic cancer accurately reflect the premorbid patterns, and partly from the technical difficulties in assaying for the particular hormones of primary interest.

## LIVER CANCER AND SEX STEROIDS

Hormones have been linked to liver tumors in men and women. The androgenic–anabolic steroids and the oral contraceptives have been implicated.

### ANDROGENIC–ANABOLIC STEROIDS AND LIVER CANCER

Androgenic–anabolic steroids in the form of oxymetholone or methyltestosterone derivatives were first linked to hepatocellular carcinoma by case reports of patients undergoing long-term therapy for aplastic anemia.[67] Patients with Fanconi's anemia seemed to be at special risk, consistent with their heritable predisposition to acute leukemia and other cancers.[68] Liver tumors also have occurred when the steroids were used for conditions other than aplastic anemia, and some tumors have regressed upon drug withdrawal. Although these findings are provocative, they are difficult to interpret because other risk factors for primary liver cancer, particularly the presence of hepatitis B virus, have not been evaluated in these studies, and they may be more common in these conditions. Resolution of these methodologic concerns was not important until the abuse of these androgenic drugs by body builders and other athletes became common (see chap 124).

### ORAL CONTRACEPTIVES AND BENIGN LIVER TUMORS

A number of clinical reports describing young women receiving oral contraceptives who developed benign liver tumors have appeared in the literature.[69] These tumors were highly vascular and often presented as emergencies with abdominal hemorrhage and shock. Two analytic case-control studies have linked these tumors to the use of oral contraceptives.[70,71] The risk for users of three to five years was about 100 times that of nonusers, and the risk for users of seven or more years about 500 times that of nonusers. The risks also appear to be higher for users over age 30, and for users of relatively high-potency pills. Although the relative risk is quite high, the absolute risk is not large for this rare tumor. The risk of hepatocellular adenoma among women under age 30 may be no more than 3:100,000 contraceptive users per year. Over this age the absolute risk probably is greater but not precisely estimated.

### ORAL CONTRACEPTIVES AND LIVER CANCER

Because of the findings of these benign tumors and the role of the liver in metabolizing steroid hormones, much concern has been expressed over the potential for a relationship between oral contraceptive use and the risk of malignant liver tumors. Thus, preliminary reports of two case-control studies of primary hepatocellular carcinoma, which indicate a duration-related excess risk of this tumor with oral contraceptive use, cause substantial concern.[72,73] Both of these studies were conducted in populations at low risk of primary liver cancer, and the excess risks were primarily seen among long-term (>8 years) users. Recently, no increased risk was noted in association with oral contraceptive use among women in high-risk populations.[73a] However, the lack of long-term users in this study makes interpretation of the apparently conflicting results difficult.

## OTHER TUMORS

For some time, there has been speculation that endogenous hormones, particularly estrogens, might figure in the etiology of *malignant melanoma*. One follow-up study and one case-control study conducted in the late 1970s implied that oral contraceptive users may be at 50% to 80% increased risk for this tumor.[74,75] Partially because of the marked rise in incidence of malignant melanoma during the 1960s and 1970s, this finding caused considerable concern. Critical reviews noted the equally impressive rise in the incidence of skin melanoma among males, and that the two positive studies had not obtained information on other possible risk factors that might be related to oral contraceptive use, particularly the duration of exposure to sunlight. Several investigations were launched to assess this issue. Although the results have been mixed, the level of concern has declined.

Also, in the late 1970s, a number of clinical series of cases of pituitary adenoma were reported among young women, a high proportion of whom had recently stopped using oral contraceptives. Subsequent investigations have indicated that this association probably was not causal, but rather reflected the increased

use of computed tomography in detection of pituitary abnormalities among women with postcontraceptive menstrual disorders.[76]

A number of other tumors have been suggested as being related to sex hormone levels because of a higher rate among females than males, a relationship to reproductive characteristics, or isolated observations of altered frequency among exogenous hormone users. In this category are cancers of the *gallbladder, thyroid, kidney, colon,* and *lung.* Most of the observations concerning these sites remain preliminary and speculative, but clearly mark these tumors as candidates for more analytical assessments in the future.

See page 1670 for References

## Ch. 226: SEX HORMONES AND HUMAN CARCINOGENESIS: EPIDEMIOLOGY


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